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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|-------------|----------------------|---------------------------------|------------------------|
| 10/807,837 | 03/24/2004 | Wenfeng Xu | 03-02 | 4419 |
| 7590 Jennifer K. Johnson ZymoGenetics, Inc. 1201 Eastlake Avenue East Seattle, WA 98102 | | | EXAMINER STOICA, ELLY GERALD | |
| | | | ART UNIT 1647 | PAPER NUMBER |
| | | | MAIL DATE 04/28/2009 | DELIVERY MODE PAPER |

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/807,837

Applicant(s)

XU ET AL.

Examiner

ELLY-GERALD STOICA

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 March 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 55-58 and 81-88 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 55-58 and 81-88 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/S5108)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/16/2009 has been entered. The pending claims are 55-58 and 81-89.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 55-58, 81-85 and 89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the independent claim 55 is drawn to an antibody comprising a monoclonal antibody. It is unclear how an antibody may *comprise* an antibody. Therefore the metes and bounds of the claims could not be determined.

In respect to claim 57 it is unclear how an antibody can be a fragment of itself. Thus the metes and bounds of the claim could not be determined.

The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 55-57 and 81-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Busfield (US 2002/0164689A1- cited previously) in view of Hopp et

al. (Hopp, TP and Woods, KR, Proc. Natl. Acad. Sci. USA: 78, 3824-28, 1981- cited previously) and in further view of Lok et al. (U.S. Pat. No. 5,965,704-cited previously) and Harlow et al. ("Antibodies-Lab Manual", Cold Spring Harbor Laboratory, 1988, ISBN 0-87969-314-2).

The claims are drawn to an antibody that specifically binds to an amino acid sequence of SEQ ID NO: 3 from amino acid number 1 (Pro), to amino acid number 6 (Asp), wherein the antibody reduces or neutralizes the activity of either IL-20 (SEQ ID NO: 8) or IL-22 (SEQ ID NO: 6). The antibody may be murine monoclonal, humanized antibody, human monoclonal or an antibody fragment. The antibody may specifically bind to the sequence mentioned above which has one conservative amino acid substitution. The antibody may be comprised in a pharmaceutical composition.

Busfield teaches an antibody that selectively binds to an isolated polypeptide consisting of a fragment of a polypeptide comprising the amino acids sequence of SEQ. ID. NO: 2 or 12, wherein the fragment comprises at least 15 contiguous amino acids of SEQ. ID. NO: 2 OR 12 (US 2002/0164689A1 § [0169]-(0181)). SEQ. ID. NO: 2 from Busfield is identical to SEQ. ID. NO: 2 of the instant application, as shown in the previous office actions, and contains sequence SEQ. ID. NO: 3 from the instant application. Busfield teaches that the antibody can be of any type of the following: polyclonal, murine monoclonal, humanized antibody, human monoclonal or an antibody fragment. Also taught are pharmaceutical compositions comprising the antibodies described. Although the sequence PEDPSD is implicitly present, Busfield does not teach making an antibody specifically against the PEDPSD hexapeptide.

Hopp et al. teach that the best antigenicity is obtained by using hexapeptides (p.3826-Table 3) and especially peptides rich in P, E and D (p.3826-Table 2). The PEDPSD hexapeptide contains the highest percentage of P, E and D of any contiguous hexapeptide of the SEQ. ID. NO: 3 of the instant application.

The hexapeptide best antigenic fragment based on a antigenicity analysis and is comprised by the longer peptide fragment of Busfield et al. Busfield does not provide a detailed analysis (just that the peptide have to be located in a hydrophilic region and the fragment has to be situated towards the surface of the polypeptide) but Hopp et al. actually offer scientific data to pick the best antigenic fragment which is present in the Seq. Id. No: 2 of Busfield et al.

Harlow et al. teach that the smallest synthetic peptides that will *consistently* elicit antibodies that bind to the original protein are 6 residues in length. The safest choice, *but also the most expensive*, will be to prepare multiple small peptides of 10-15 amino acids in length from various regions of the sequence (Harlow et al., p76, subtitle "Size of the peptide").

Lok et al. (column 15, lines 14-24) teaches the use of Zcytor11 (SEQ. ID. NO: 2) polypeptides for preparing antibodies (polyclonal, murine monoclonal, or an antibody fragment) that bind to Zcytor11, which has a sequence identical to sequence SEQ. ID. NO: 2 from the application (the full 574 amino acid sequence). Also contemplated were neutralizing antibodies to Zcytor 11 (col.15, lines 57-60). Zcytor11 is an alternative name given to the IL-22 RA, which is a receptor subunit for both IL-20 and IL-22 as presented also in the instant Application.

The limitations that the antibody against the IL-22 RA reduces or neutralizes the activity of either IL 20 or IL-22 or both are inherently present as a consequence of the structure of the antibody.

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to use the best antigenic features (as taught by Hopp et al.) to make antibodies as taught by Busfield and Lok and to obtain neutralizing antibodies as suggested by Lok et al. with a reasonable expectation of success. As an extra motivator for choosing the hexapeptide instead of longer sequence is offered by Harlow et al. which showed that the shortest sequence that performed consistently was a hexapeptide and this approach is cheaper than trying longer stretches of amino acids. A person of ordinary skill in the art has always a good reason to pursue the known options (as articulated by Hopp et al. and prodded by Lok et al.) within her or his technical grasp. If this leads to the anticipated success, it is more likely the product not of innovation but of the ordinary skill and common sense.

8. Applicant's arguments filed 03/16/2009 have been fully considered but they are not persuasive. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a

reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

9. On page 5 of the Remarks Applicant argues that Busfield teaches antigenic peptides comprising at least 8 amino acid residues and therefore by singling out a hexapeptide is impermissible hindsight. The arguments were carefully considered but not found persuasive because, as presented above, Harlow et al. taught the hexapeptide unit as consistently being used to raise antibodies and a person of ordinary skill in the art may be motivated by cost considerations to choose the hexapeptide.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

On page 5-7 of the Remarks Applicant argues combining Hopp et al. with Busfield is not a valid establishment of obviousness. In Applicant's view, the Examiner's position is flawed because Examiner misunderstood the Hopp et al. reference. The arguments were carefully considered but not found persuasive because Hopp et al. teach that antigenic determinants are surface features of proteins and indicate that they are frequently found on regions of a molecule that have an unusually high degree of exposure to solvent- i.e., regions which project into the medium. Also, charged hydrophilic amino acid side chains are common features of antigenic determinants, and

also that those regions lacked large hydrophobic residues. The reason that the hexapeptides were chosen is because this is the size of an antigenic determinant. It is considered that it is irrelevant that, as alleged by Applicant, the antigenic determinant considered by Hopp et al. must have been greater than 6 residues. Once again, applicants are arguing the references separately, rather than in the combination in which they were cited. As such the Harlow et al. reference would lead a person of ordinary skill in the art at least to consider hexapeptides.

On page 7 of the Remarks Applicant argues that an application of the Hopp et al. techniques to the sequence of IL-22 RA would teach away from considering the sequence "PEDPSD" and consider first and the hexameric sequence that would have the most favorable score is "KQREYE" (amino acids 165-170 in SEQ ID NO: 3 or 182-187 in SEQ ID NO: 2). The arguments were carefully considered but not found persuasive because even if considering *in arguendo* that by Applying Hopp et al. a person of ordinary skill in the art would find the "KQREYE" hexapeptide to be the most favorable, the teachings of Hopp et al. would still suggest to a person of ordinary skill in the art to use second and third highest points. This rationale is considered for a generic polypeptide. However, when combined with the requirements that the epitope has to be exposed to the surface and in a hydrophilic region, it is more likely than not that this region would be at the N-terminal part of the extracellular receptor where it also has a higher exposure to the surface than closer to the transmembrane region, where the "KQREYE" sequence is situated. It is not required that the claimed embodiment be the most preferred embodiment suggested by the references.

On page 7 of the Remarks Applicant argues that Hopp et al. did not teach an emphasis on peptides rich in Proline. The arguments were carefully considered but not found persuasive because first of all, this is considered a misinterpretation of Hopp et al. because by considering the table 2 and 3 of the reference, Hopp et al. shows the improvement that is obtained when the peptide contains proline. The peptide containing proline in the table has the highest correct prediction rate with no wrong predictions. The value for P in the table is adjusted to zero. Again, when compared to peptides of variable length, the best predictions are obtained for hexapeptides containing P, E, and D with no wrong predictions (Table 3). Taken in this context, by applying the teaching of Hopp et al., one would have to consider the improvement brought about by the presence of the Proline and as such the KQREYE sequence would not have been considered the best option in view of the references.

Applicant interpreted the Hopp et al. reference as optimizing the sequence length to six amino acids as opposed to seven amino acids considered in a previous study. This argument was carefully considered but not found persuasive because this is considered a selective reading of the reference. When the whole reference is read, it appears clearly that the best results are obtained with hexapeptides containing the highest percentage of P, E and D.

10. Claim 58 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Busfield (US 2002/0164689A1 in view of Hopp et al. (Hopp, TP and Woods, KR, Proc. Natl. Acad. Sci. USA: 78, 3824-28, 1981) and in further view of Lok et al. (US Patent

5,965,704.), Harlow et al. ("Antibodies-Lab Manual", Cold Spring Harbor Laboratory, 1988, ISBN 0-87969-314-2) and Gonzales et al. (U. S. Pat. No. 6,133,426).

Claim 58 adds the limitation that the claimed antibody is PEGylated.

The teachings of Busfield, Hopp et al. Lok et al. and Harlow et al. were presented *supra*. None of them contemplate PEGylating the antibodies.

Gonzales et al. teach humanized anti-IL-8 monoclonal antibodies and variants thereof for use in diagnostic applications and in the treatment of inflammatory disorders. Also described is a conjugate formed by an antibody fragment covalently attached to a non-proteinaceous polymer (PEG). The conjugate exhibits substantially improved half-life, mean residence time, and/or clearance rate in circulation as compared to the underivatized parental antibody fragment.

Busfield teaches pharmaceutical compositions comprising antibodies and it would have been obvious to one of ordinary skill in the art at the time of the invention to modify by PEGylation the antibodies of either of Busfield or Lok et al. (raised as in view of Hopp et al. and Harlow et al.) in order to increase the serum half-life, as taught by Gonzales et al. with a reasonable expectation of success because Gonzales suggested and described the benefits of PEGylated antibodies for therapy.

Applicants' arguments pertaining to the instant rejection are largely duplicative of those to the rejection above, and are believed to have been fully considered above.

Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 9:00-18:30 M-Th and 9:00-18:30 alternate F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Lorraine Spector, Ph.D.
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